Mechanisms of TGFbeta inhibition of LUNG endodermal morphogenesis: the role of TbetaRII, Smads, Nkx2.1 and Pten.

Journal: Dev Biol

Publication Year: 2008

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PubMed link: 18602626

Funding Grants: CIRM Stem Cell Biology Training Grant

Public Summary:
In summary, the TGFβ-induced inhibition of lung endodermal morphogenesis appears to entail at least two related mechanisms. First, TGFβ, via stimulation of the transcription factor EGR1 and its target gene, Pten has a profound inhibitory effect on endodermal cell proliferation. Inhibition of cell proliferation undoubtedly slows, if not block morphogenesis. In addition, however, TGFβ has a direct impact on morphoregulatory genes, such as Nkx2.1 and Bmp4, two molecules that are absolutely required for endodermal morphogenesis. Both of the latter mechanisms are dependent on intact TβRII-mediated signaling. The partial role of SMADs in this pathway is a novel finding that indicates a key role for alternative, SMAD-independent TGFβ signaling pathways.

Scientific Abstract:
Transforming growth factor-beta is a multifunctional growth factor with roles in normal development and disease pathogenesis. One such role is in inhibition of lung branching morphogenesis, although the precise mechanism remains unknown. In an explant model, all three TGFbeta isoforms inhibited FGF10-induced morphogenesis of mesenchyme-free embryonic lung endoderm. Inhibition of budding by TGFbeta was partially abrogated in endodermal explants from Smad3(-/-) or conditional endodermal-specific Smad4(Delta/Delta) embryonic lungs. Endodermal explants from conditional TGFbeta receptor II knockout lungs were entirely refractive to TGFbeta-induced inhibition. Inhibition of morphogenesis was associated with dedifferentiation of endodermal cells as documented by a decrease in key transcriptional factor, NKX2.1 protein, and its downstream target, surfactant protein C (SpC). TGFbeta reduced the proliferation of wild-type endodermal cells within the explants as assessed by BrdU labeling. Gene expression analysis showed increased levels of mRNA for Pten, a key regulator of cell proliferation. Conditional, endodermal-specific deletion of Pten overcame TGFbeta's inhibitory effect on cell proliferation, but did not restore morphogenesis. Thus, the mechanisms by which TGFbeta inhibits FGF10-induced lung endodermal morphogenesis may entail both inhibition of cell proliferation, through increased Pten, as well as inhibition or interference with morphogenetic mediators such as Nkx2.1. Both of the latter are dependent on signaling through TbetaRII.